UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,098	12/12/2003	Annika Margareta Pettersson-Fernholm	B45106C1	2512

7590 01/28/2005

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939

EXAMINER	
GRASER, JENNIFER E	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 01/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/735,098	PETTERSSON-FERNHOLM ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-55* is/are pending in the application.

4a) Of the above claim(s) *40-52,54 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-39 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/485,760.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

1. Acknowledgment and entry of the Amendment submitted on 12/10/04 is made. Claims 35-39 and 53 are currently under examination. Claims 40-52, 54 and 55 were previously withdrawn.

Applicant's arguments and amendments have overcome the former 112, second paragraph rejections.

Claim Rejections - 35 USC 112- first paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 35-39 and 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "an isolated polynucleotide encoding *Neisseria meningitidis* LbpB selected from the group consisting of: SEQ ID NO:1 (nucleotide 100-nucleotide2274), SEQ ID NO: 3, SEQ ID NO:5, SEQ ID NO:7, or SEQ ID NO:9' and for an isolated polynucleotide which encodes the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, or SEQ ID NO:10' and host cells and test kits comprising the polynucleotide sequences, does not reasonably provide enablement for "An isolated polynucleotide encoding a *Neisseria*

polynucleotide sequence that is at least 90% identical to that of SEQ ID NO:1 (nucleotide 100-nucleotide2274), SEQ ID Nos: 3, 5, 7, or 9", nor is it enabled for methods of making a protein using these polynucleotides of for test kits for diagnosing neisserial bacteria in a human which comprise these polynucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The breadth of the instant claims contain nucleotide sequences other than what is specified in the sequence disclosure. The specification states that substitutions, additions, or deletions may be made to the defined sequences; however, the specification provides no guidance as to what nucleotides may be changed without causing a detrimental effect to the protein to be produced. Further, it is unpredictable as to which nucleotides could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein' sequence where amino acid substitutions can be made with a reasonable

expectation of success are limited. Other positions are critical to the protein' structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. Applicants have provides no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different nucleotide substitutions and the nature and extent of the changes that can be made.

It is well known in the prior art that selective point mutation to one key amino acid residue eliminate the ability of an antibody to recognize this altered protein. If the range of decreased binding ability after single point mutation of a protein varies one could expect point mutations in the protein antigen to cause varying degrees of loss of function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. A nucleotide sequence with 10% random difference may very well lose the ability to bind to human lactoferrin as required by the claims and is unlikely to produce a functional LbpB polypeptide as required by the claims. Additionally, a polynucleotide sequence with a 10% difference will not function as a reliable detection agent in a kit for diagnosing infection with neisserial bacteria. To start with the DNA sequence first, this requires even more work on the part of the skilled

artisan. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed. See Mikayama et al. (Nov.1993. Proc.Natl.Acad.Sci. USA, vol. 90 : 10056-10060) which teaches that the three-dimensional structure of molecules is important for their biological function and even a single amino acid difference may account for markedly different biological activities. Rudinger et al. (June 1976. Peptide Hormones. Biol.Council. pages 5-7) also teaches that amino acids owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study.

Applicants have provide no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different nucleotide substitutions and the nature and extent of the changes that can be made. Given the lack of guidance contained in the specification and the unpredictability for determining acceptable nucleotide substitutions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Response to Applicants' Arguments:

Applicants argue that routine experimentation is permitted, particularly when there is a reasonable amount of guidance provided in the specification. They argue that amino acids 160-162 could be changed from KWT to EWT or EQN without affecting the

activity of the LbpB and, therefore, it is shown that the skilled artisan can design polypeptides encoding LbpB with sequences up to at least 90% identity difference. This has been fully and carefully considered but is not deemed persuasive. First, the example provided is not to a sequence which is 90% different, e.g., there is only 1-3 changes. A 90% difference to SEQ ID Nos: 1, 3, 5, 7 or 9 is at least 20 nucleotides or 6+ amino acids. This isolated example does not enable the broader scope. As stated in the rejection above, changes in amino acids amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study. Starting with the nucleic acid sequences requires even more work. This is not 'routine experimentation', but is undue experimentation. The three-dimensional structure of molecules is important for their biological function and even a single amino acid difference may account for markedly different biological activities.

Claim Rejections - 35 USC 112-Written Description

4. Claims 35-39 and 53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:1(from nucleotide 100 to nucleotide 2274), 3, 5, 7 and 9 and equivalent degenerative codon sequences thereof, i.e., isolated polynucleotides encoding the amino acid sequence set forth in SEQ ID Nos: 2, 4, 6, 8 or 10, and therefore the written description is not commensurate in scope with the claims

which are broadly drawn to any isolated polynucleotide encoding N.meningitidis LbpB (claim35) and polynucleotides which vary by 20% of the known sequences.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID Nos:1 (from nucleotide 100 to nucleotide 2274), 3, 5, 7, and 9 and the degenerates thereof, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic

acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

However, no disclosure, beyond the mere mention of allelic variants is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only an isolated polynucleotide comprising SEQ ID NO:1 (from nucleotide 100 to nucleotide 2274), 3, 5, 7 and 9 and equivalent degenerative codon sequences thereof, i.e., isolated polynucleotides encoding the amino acid sequence set forth in SEQ ID Nos: 2, 4, 6, 8 or 10, but not the full breadth of the claims meets the written description provisions of 35 USC 112, first paragraph.

Response to Applicants' Arguments:

Applicants argue that since they are not identifying their polynucleotides by "function", but merely by 'identity' that the Reagents of the Univ. Calif. V. Eli Lilly case does not presently apply. This has been fully and carefully considered but is not deemed persuasive. First, a polynucleotide sequence must have a function. Second, the claims recite that the polynucleotide "encodes *Neisseria meningitidis* LbpB". This is an asserted function. Applicants cannot blindly assign a algorithm to determine what may be encompassed in their claims because this does not provide adequate written description. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. Therefore only an isolated polynucleotide comprising SEQ ID NO:1 (from nucleotide 100 to nucleotide 2274), 3, 5, 7 and 9 and equivalent degenerative codon sequences thereof, i.e., isolated polynucleotides encoding the amino acid sequence set forth in SEQ ID Nos: 2, 4, 6, 8 or 10, but not the full breadth of the claims, e.g., any sequences which are at least 90% identical to SEQ ID NO:1 (from nucleotide 100 to nucleotide 2274), 3, 5, 7 and 9, meets the written description provisions of 35 USC 112, first paragraph.

Allowable Subject Matter

5. An isolated polynucleotide consisting of SEQ ID Nos: 1 (from nucleotide 100 to nucleotide 2274), 3, 5, 7 or 9 is free of the prior art.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 872-9306 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

J Graser 1/27/05

Jennifer Graser
Primary Examiner
Art Unit 1645